

REMARKS

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks.

Claims 3 and 23 are amended herein to correct minor informalities. No new matter has been added by the amendments presented herein.

Request for Reconsideration and Removal of Office Action Finality

The application has been finally rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to practice the invention commensurate in scope with the claims. Applicants respectfully traverse the imposition of finality.

MPEP § 706.07(a), mandates that second actions on the merits can properly be made final, *except* where the Examiner introduces a new ground of rejection that is neither necessitated by Applicants' amendment nor based on information submitted in an information disclosure statement (IDS). The outstanding rejection of claims 1-4, 6, 10, 17, 19-23, and 30 under 35 U.S.C. § 112, first paragraph, based on the alleged insufficiency of Applicants Specification, which shows optimization of expression in human 293 cells, in providing enablement for claims drawn to optimization of expression in "any cell of a human host" (*see* Office Action, page 3) was presented for the first time in the current Office Action, mailed September 22, 2004. Because the previous office actions have not rejected the above-referenced claims as non-enabled based on the argument above, Applicants have not had an opportunity to respond to this rejection, which was not necessitated by Applicants' amendment of the claims nor based on an IDS submitted by Applicants. Therefore, Applicants submit that finality of the present Office Action is improper.

Because the currently outstanding enablement rejection represents a new ground for rejection, the final rejection of these claims is not consistent with the requirements of final rejection set forth in MPEP 706.07(a). Accordingly, Applicants respectfully request the reconsideration and removal of the imposition of finality of the rejection and request that the current response be treated as a response under 37 C.F.R. § 1.111.

Claim Objections

Claim 3 is objected to because the claim number from which the claim depends is absent. In response thereto, Applicants have amended claim 3 to indicate dependence on claim

2. Accordingly, Applicants assert that claim 3 is in condition for allowance and respectfully request that the objection be removed and the claims allowed.

Claim 23 is objected to because, according to the Office Action, a comma should be inserted before the “wherein” phrase. In response thereto, Applicants have amended the above-referenced claim to insert a comma before the “wherein” phrase. Accordingly, Applicants assert that claim 23 is in condition for allowance and respectfully request that the objection be removed and the claims allowed.

Rejections under 35 U.S.C. § 112, Paragraph One

Claims 1-4, 6, 10, 17, 19-23, and 30 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to make and use the invention commensurate in scope with the cited claims. Specifically, the Office Action states that the specification, “while being enabling for making and using a synthetic polynucleotide comprises (*sic*) SEQ ID Nos: 1, 2, 3, or 4, which are codons optimized for expression in human 293 cells, does not reasonably provide enablement for making and using a synthetic polynucleotide comprising unspecified codon that are optimized for expression in any cell of a human host.” *See* Office Action at page 3, paragraph 2. Applicants respectfully traverse.

The Supreme Court has interpreted the enablement requirement set forth in the first paragraph of § 112 to require that, at the time of filing, one of skill in the art is able to practice the claimed invention without undue or unreasonable experimentation. *Mineral Separation v. Hyde* 242 U.S. 261, 270 (1916). The Office Action states that the “most relevant” factors to consider when determining whether the amount of experimentation needed to practice the claimed invention is undue are:

the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

See Office Action at page 3, lines 18-21. At the outset, Applicants note that the current Office Action concedes that the Specification provides teaching methods for obtaining optimized codons and that “the claimed genus of codons could be made by the teaching of the specification.” *See* Office Action at page 4, lines 5-6.

However, the Examiner takes the position that the rejected claims are not enabled because (1) codon optimization is not always successful at increasing expression of a particular

gene and successful codon optimization of one gene is not predictive of the future success of a different gene and (2) successful optimization of a gene expressed in human 293 cells is not predictive of successful optimization of that gene in other human cells.

With respect to point 1, the Examiner alleges that the Declaration of William L. McClements, (hereinafter McClements declaration) supports the contention that codon optimization is “not predictable (*sic*) of future success from one gene to the other” and specifically cites point 6 of the McClements declaration. Applicants respectfully disagree with this statement and submit that point 6 of the McClements declaration does not state that codon optimization is not predictive of future success from one gene to the other. It clearly states “codon-optimization is not always successful at producing increased gene expression in a cell type of interest and that codon-optimization *of one virus* is not predictive of future success *with a different virus*.” See McClements declaration, point 6. The declaration further points out that none of the references cited in support of the previous § 103 rejection teaches codon optimization of HPV-16 genes, and, therefore, it was not known that codon-optimization of HPV-16 genes would be successful prior to the present invention.

The Office Action further alleges that the McClements declaration states at point 7, that “the presence of inhibitory sequences is unique for different genes.” See Office Action at page 4, lines 17-19. Applicants respectfully disagree with the contention that the declaration makes such a statement and request that the Examiner cite the specific lines in point 7 where that statement appears. Point 7 of the declaration clearly asserts that art existed at the time of filing which would lead one to believe that HPV 16 gene expression is limited by transcriptional regulation and mRNA instability, not codon usage. Upon a complete reading of points 6 and 7 of the declaration, one can see that the declarant was making the point that although the Frazer reference (cited in the previous § 103 rejection) discussed codon-optimization of late genes from BPV-1, it was not indicative of an expectation of success of codon-optimization of HPV-16 genes because (a) BPV-1 and HPV-16 are different viruses that cause different diseases (*see* point 6 of the declaration) and (b) the art that existed at the time of filing would lead one of skill in the art to believe that HPV16 gene expression, but not BPV-1 gene expression, is limited by transcriptional regulation and mRNA instability (*see* point 7 of the declaration).

With respect to point 2 of the Examiner’s argument above, The Office Action alleges that the McClements declaration supports the contention that successful optimization of a gene expressed in human 293 cells is not predictive of successful optimization of that gene in other human cells. Applicants respectfully disagree with this statement and request that the Examiner cite the specific lines in the declaration that state that 293 cells do not behave similarly and/or are not predictive of other human cells. Upon reviewing the outstanding Office Action,

Applicants note that the Office Action fails to cite any evidence for the statement that human 293 cells do not behave similarly to other human cells. Given the lack of objective evidence presented in the Office Action to support this assertion, Applicants respectfully request that the Examiner submit an affidavit pursuant to 37 C.F.R. § 1.104(d)(2), detailing personal facts or knowledge relied on in reaching this conclusion.

As stated in Applicants' specification, the present invention provides HPV gene segments which were converted to sequences having identical translated sequences but with alternative codon usage as defined by Lathe, 1985 "Synthetic Oligonucleotide Probes Deduced from Amino Acid Sequence Data: Theoretical and Practical Considerations" *J. Molec. Biol.* 183:1-12. The Lathe article defines optimal codons for high expression in *human* cells. Contrarily, if one desired to optimize expression of a gene in a different type of cell, such as an *E. coli* cell or a yeast cell, then the codons found in highly expressed human genes, which are set forth in the Lathe article, would not be a good choice.

Applicants respectfully submit that the full scope of the present claims is enabled by Applicants specification, as conceded in the Office Action. (See Office Action at page 4, lines 5-6, stating: "the claimed genus of codons could be made by the teaching of the specification.") Applicants further submit that the disclosure exemplifies novel codon-optimized polynucleotides encoding HPV16 proteins, which are particular embodiments within the scope of the claims, and also teaches how one of skill in the art can obtain other embodiments within the scope of the claims. Thus, it is Applicants position that it would not require undue experimentation to practice the claimed invention.

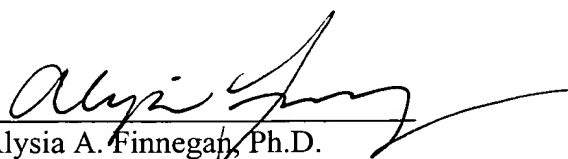
Accordingly, Applicants assert that claims 1-4, 6, 10, 17, 19-23, and 30, are in condition for allowance and respectfully request that the rejection of these claims be removed and the claims allowed.

Summary

Applicants respectfully submit that all outstanding rejections have been overcome by the amendments herein and remarks above. Accordingly, Applicants maintain all claims are in condition for allowance and a favorable action on the merits is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, she is requested to call the undersigned counsel at the number listed below.

Respectfully submitted,

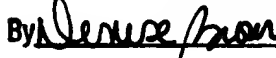
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Date: December 21, 2004

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

MERCK & CO., INC.

By  Date 12-22-2004